

### REMARKS

Claims 22-44 are pending in this application. Claim 24 has been rejected under 35 U.S.C. § 112, first paragraph, for overbreadth, and under 35 U.S.C. § 112, second paragraph, for lack of clarity. Claims 22-44 are rejected under 35 U.S.C. § 103(a) for obviousness over Yamamura et al. (Japanese Journal of Pharmacology 65:289-291, 1994; hereinafter “Yamamura”) in view of Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter “Gerhart”) and Constantz et al. (U.S. Patent No. 5,782,971; hereinafter “Constantz”). Claims 22-44 are provisionally rejected for obviousness-type double patenting over claims 22-44 of copending U.S. Serial No. 09/692,664. By this reply, Applicants amend claims 24 and 36, and address the Examiner's rejections below.

#### Support for the Amendment

Claim 24 has been amended to remove the phrase “derivatives thereof”. Claim 36 has been amended to correct a typographical error. No new matter is added by the amendment.

#### Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects claim 24 under 35 U.S.C. § 112, first paragraph, for overbreadth. The Examiner states that “the recitation of ‘derivatives thereof’ encompass a plethora of compounds, the scope of which is not enabled.” (Office Action, p. 2.) Applicants have amended claim 24 to remove the phrase “derivatives thereof.” Therefore, this rejection should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claim 24 under 35 U.S.C. § 112, second paragraph, for indefiniteness, stating that the “recitation of ‘derivatives thereof’ in claim 24 renders the claim indefinite. (Office Action, p. 3.) As is stated above, Applicants have removed the phrase “derivatives thereof” from claim 24, and this rejection can now be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 22-44 stand rejected under 35 U.S.C. § 103(a) for obviousness over Yamamura in view of Gerhart and Constantz. The Examiner states:

Yamamura discloses methods of implanting injectable doxorubicin loaded hydroxyapatite beads for treating tumor...Gerhard disclose calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration...Constantz et al. teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles...Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Yamamura’s composition into an injectable paste, as suggested by Gerhard and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest such as a tumor... (Office Action, pp. 3 and 4.)

Applicants respectfully traverse this rejection.

The M.P.E.P. § 2143 states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference

(or references when combined) must teach or suggest all the claim limitations.

A *prima facie* case of obviousness requires that all three criteria set forth in M.P.E.P. § 2143 be met. For the reasons provided below, the combination of Yamamura, Gerhart, and Constantz fails to teach or suggest all of the claim limitations of present claims 22-44 and, in addition, Gerhart and Constantz fail to provide any motivation to modify the disclosure of Yamamura to yield the invention of present claims 22-44.

The Combination of Yamamura, Gerhart, and Constantz Fails to Teach or Suggest All Claim Limitations

Yamamura discloses the use of an adriamycin (ADR; i.e., doxorubicin)-loaded hydroxyapatite (HAP) bead for treating a chondrosarcoma in Sprague-Dawley rats (see, e.g., Yamamura, abstract). As is acknowledged by the Examiner, Yamamura fails to teach or suggest a paste formulation for the ADR-loaded HAP bead (see Office Action, p. 3). More than that, Yamamura fails to teach or suggest a composition composed of a calcium phosphate paste in combination with an anticancer agent that has an injectable or formable consistency at the time of administration, as is recited in present claims 22-44. Therefore, Yamamura fails to teach or suggest all the elements of present claims 22-44. To remedy the deficiencies of Yamamura, the Examiner has cited Gerhart and Constantz. These references, alone or in combination with Yamamura, fail to teach or suggest a composition comprising a calcium phosphate paste in combination with an anticancer agent.

Gerhart and Constantz do not Remedy the Deficiencies of Yamamura

The Examiner relies on Gerhart and Constantz to provide the claim limitations missing in Yamamura. But, like Yamamura, neither Gerhart nor Constantz teaches or suggests a composition comprising a calcium phosphate paste in combination with an anticancer agent.

Gerhart describes a “bone cement...comprised of a particulate biocompatible calcium phosphate ceramic and particulate resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix...[that can be] used for bone/implant fixation, or as a filler or cement for bone repair.” (See the Abstract.) Gerhart also discloses that an antibiotic can be incorporated into the cross-linked biodegradable matrix (col. 4, lines 30-34, and col. 10, lines 48-54). Gerhart does not teach or suggest incorporation of an anticancer agent into the bone cement.

The Examiner states that “Gerhart’s compositions contain active agents that are readily used in treatment of cancers such as bone tumor.” This is incorrect. Gerhart’s bone cement is employed to fill bone cavities that remain after the excision of bone during the treatment of bone tumors (see col. 13, lines 45-49). As is discussed above, Gerhart discloses that an antibiotic can be incorporated into the bone cement, but fails to teach or suggest that the addition of the antibiotic is for the treatment of cancer. Gerhart contains absolutely nothing to suggest the combination of a calcium phosphate paste with an anticancer agent. Accordingly, Gerhart cannot be used to remedy the deficiencies of Yamamura.

Constantz also fails to remedy the deficiencies of Yamamura and Gerhart. Constantz merely discloses a calcium phosphate cement composition that may contain, for example, an antibiotic or a protein (see, e.g., col. 5, line 57, though col. 6, line 11). Constantz lacks any teaching or suggestion that the protein is an anticancer agent, or that an anticancer agent should

be combined with the calcium phosphate cement composition, as is acknowledged by the Examiner (Office Action, page 4).

For all of the above reasons, none of Yamamura, Gerhart, and Constantz, alone or in combination, teaches or suggests a calcium phosphate paste containing an anticancer agent. Therefore, the combination of these references cannot serve as the basis for a rejection of claims 22-44 under 35 U.S.C. § 103(a) (M.P.E.P. § 2143, *supra*).

Gerhart and Constantz do not Provide Any Motivation to Modify the Teachings of Yamamura

The Examiner also argues that Gerhart and Constantz provide the skilled artisan with the motivation to modify Yamamura, stating:

...it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Yamamura's composition into an injectable paste, as suggested by Gerhard and Constanz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest such as a tumor. (Office Action, p. 4.)

Applicants respectfully disagree.

The M.P.E.P. § 2143.01 states:

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." (Citations omitted.)

Yamamura discloses the use of an ADR-loaded HAP bead, but fails to teach or suggest

that the HAP bead could be provided in any other form (e.g., as a calcium phosphate paste).

Gerhart and Constantz do not provide any motivation to modify Yamamura's HAP bead to yield the presently claimed calcium phosphate paste composition, because they merely disclose the use of a calcium phosphate cement composition that contains an antibiotic or, as is also disclosed in Constantz, a protein. Neither reference, either explicitly or implicitly, teaches or suggests that an anticancer agent could be used in place of the antibiotic/antimicrobial agent. Absent this disclosure, the skilled artisan would have no motivation to modify Yamamura based on Gerhart and Constantz to yield the invention of present claims 22-44 (M.P.E.P. § 2143.01, *supra*). For this reason as well, the combination of these references cannot serve as the basis for a rejection of claims 22-44 under 35 U.S.C. § 103(a) for obviousness, and Applicants respectfully request that this rejection be withdrawn.

Claims 42-44 are Not Obvious in View of Yamamura in Combination with Gerhart and Constantz

Claims 42-44 stand rejected under 35 U.S.C. § 103(a) over Yamamura in combination with Gerhart and Constantz. The Examiner states that, based on the combination of Yamamura, Gerhart, and Constantz, "the ordinary artisan would have had a reasonable expectation of success in preparing a ready to use kit for easing the access and use of such compositions at a clinical setting." Applicants respectfully traverse this rejection.

As is discussed above, none of Yamamura, Gerhart, or Constantz, alone or in combination, teaches or suggests a calcium phosphate paste containing an anticancer agent. Therefore, the cited references also fail to teach or suggest the preparation of a ready to use kit

containing such a composition, as is recited in present claim 42, and claims dependent therefrom.

Furthermore, as is discussed above with respect to claim 22, and claims dependent therefrom, neither Gerhart nor Constantz provides any motivation to modify Yamamura to yield a calcium phosphate paste containing an anticancer agent. Therefore, Gerhart and Constantz also fail to provide the necessary motivation to modify Yamamura to yield the kit of present claims 42-44. For all the reasons provided above, the requirements for establishing a *prima facie* case of obviousness against claims 42-44 have not been met (M.P.E.P. § 2143, *supra*). Accordingly, Applicants respectfully request that this rejection be withdrawn.

#### Provisional Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejects claims 22-44 for obviousness-type double patenting over claims 22-44 of copending Application Serial No. 09/692,664, stating:

Although the conflicting claims are not identical, they are not patentably distinct from each other because both claimed inventions are directed towards compositions comprising calcium phosphate and an anticancer agent. Office Action, p. 9.

In response to the provisional double patenting rejection of claims 22-44 over claims 22-44 of copending Application Serial No. 09/692,664, Applicants will submit a terminal disclaimer, if necessary, to overcome the rejection once otherwise allowable subject matter has been determined.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for two months, to and including October 21, 2003, and a check for the fee required under 37 C.F.R. § 1.17(a). If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date:

Oct 15, 2003

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